



4164-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 866

[Docket No. FDA-2019-N-5192]

Microbiology Devices; Reclassification of Human Immunodeficiency Virus Serological
Diagnostic and Supplemental Tests and Human Immunodeficiency Virus Nucleic Acid
Diagnostic and Supplemental Tests

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed amendment; proposed order.

SUMMARY: The Food and Drug Administration (FDA or the Agency) is proposing to reclassify certain human immunodeficiency virus (HIV) serological diagnostic and supplemental tests and HIV nucleic acid (NAT) diagnostic and supplemental tests, postamendments class III devices with the product code MZF, into class II (special controls), subject to premarket notification. FDA is also proposing new device classification regulations along with special controls that the Agency believes are necessary to provide a reasonable assurance of safety and effectiveness for these devices. FDA is proposing this reclassification on its own initiative. If finalized, this order will reclassify these types of devices from class III (premarket approval) to class II (special controls) and reduce the regulatory burdens associated with these devices, as these types of devices will no longer be required to submit a premarket approval application (PMA) but can instead submit a premarket notification (510(k)) and receive clearance before marketing their device.

DATES: Submit either electronic or written comments by [INSERT DATE 60 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL REGISTER*]. Please see section XI of this document for the proposed effective date when the new requirements apply and for the proposed effective date of a final order based on this proposed order.

ADDRESSES: You may submit comments as follows. Please note that late, untimely filed comments will not be considered. Electronic comments must be submitted on or before [INSERT DATE 60 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL REGISTER*]. The <https://www.regulations.gov> electronic filing system will accept comments until 11:59 p.m. Eastern Time at the end of [INSERT DATE 60 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL REGISTER*]. Comments received by mail/hand delivery/courier (for written/paper submissions) will be considered timely if they are postmarked or the delivery service acceptance receipt is on or before that date.

Electronic Submissions

Submit electronic comments in the following way:

- Federal eRulemaking Portal: <https://www.regulations.gov>. Follow the instructions for submitting comments. Comments submitted electronically, including attachments, to <https://www.regulations.gov> will be posted to the docket unchanged. Because your comment will be made public, you are solely responsible for ensuring that your comment does not include any confidential information that you or a third party may not wish to be posted, such as medical information, your or anyone else's Social Security number, or confidential business information, such as a manufacturing process. Please note that if you include your name, contact information, or other information that identifies you in

the body of your comments, that information will be posted on

<https://www.regulations.gov>.

- If you want to submit a comment with confidential information that you do not wish to be made available to the public, submit the comment as a written/paper submission and in the manner detailed below (see "Written/Paper Submissions" and "Instructions").

Written/Paper Submissions

Submit written/paper submissions as follows:

- Mail/Hand delivery/Courier (for written/paper submissions): Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.
- For written/paper comments submitted to the Dockets Management Staff, FDA will post your comment, as well as any attachments, except for information submitted, marked and identified, as confidential, if submitted as detailed in "Instructions."

Instructions: All submissions received must include the Docket No. FDA-2019-N-5192 for "Microbiology Devices; Reclassification of human immunodeficiency virus serological diagnostic and supplemental tests and human immunodeficiency virus nucleic acid diagnostic and supplemental tests". Received comments, those filed in a timely manner (see ADDRESSES), will be placed in the docket and, except for those submitted as "Confidential Submissions," publicly viewable at <https://www.regulations.gov> or at the Dockets Management Staff between 9 a.m. and 4 p.m., Monday through Friday.

- Confidential Submissions--To submit a comment with confidential information that you do not wish to be made publicly available, submit your comments only as a written/paper submission. You should submit two copies total. One copy will include the information

you claim to be confidential with a heading or cover note that states "THIS DOCUMENT CONTAINS CONFIDENTIAL INFORMATION." The Agency will review this copy, including the claimed confidential information, in its consideration of comments. The second copy, which will have the claimed confidential information redacted/blacked out, will be available for public viewing and posted on <https://www.regulations.gov>. Submit both copies to the Dockets Management Staff. If you do not wish your name and contact information to be made publicly available, you can provide this information on the cover sheet and not in the body of your comments and you must identify this information as "confidential." Any information marked as "confidential" will not be disclosed except in accordance with 21 CFR 10.20 and other applicable disclosure law. For more information about FDA's posting of comments to public dockets, see 80 FR 56469, September 18, 2015, or access the information at:

<https://www.govinfo.gov/content/pkg/FR-2015-09-18/pdf/2015-23389.pdf>.

Docket: For access to the docket to read background documents or the electronic and written/paper comments received, go to <https://www.regulations.gov> and insert the docket number, found in brackets in the heading of this document, into the "Search" box and follow the prompts and/or go to the Dockets Management Staff, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.

FOR FURTHER INFORMATION CONTACT: Jenifer Roe, Center for Biologics Evaluation and Review, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 71, Rm. 7301, Silver Spring, MD 20993-0002, 240-402-7911.

SUPPLEMENTARY INFORMATION:

I. Background--Regulatory Authorities

The Federal Food, Drug, and Cosmetic Act (FD&C Act), as amended by the Medical Device Amendments of 1976 (the 1976 amendments) (Pub. L. 94-295), the Safe Medical Devices Act of 1990 (Pub. L. 101-629), Food and Drug Administration Modernization Act of 1997 (Pub. L. 105-115), the Medical Device User Fee and Modernization Act of 2002 (Pub. L. 107-250), the Medical Devices Technical Corrections Act (Pub. L. 108-214), the Food and Drug Administration Amendments Act of 2007 (Pub. L. 110-85), and the Food and Drug Administration Safety and Innovation Act (Pub. L. 112-144), among other amendments, establishes a comprehensive system for the regulation of medical devices intended for human use. Section 513 of the FD&C Act (21 U.S.C. 360c) established three categories (classes) of devices, reflecting the regulatory controls needed to provide reasonable assurance of their safety and effectiveness. The three categories of devices are class I (general controls), class II (general controls and special controls), and class III (general controls and premarket approval).

Section 513(a)(1) of the FD&C Act defines the three classes of devices. Class I devices are those devices for which the general controls of the FD&C Act (controls authorized by or under sections 501, 502, 510, 516, 518, 519, or 520 (21 U.S.C. 351, 352, 360, 360f, 360h, 360i, or 360j) or any combination of such sections) are sufficient to provide reasonable assurance of safety and effectiveness; or those devices for which insufficient information exists to determine that general controls are sufficient to provide reasonable assurance of safety and effectiveness or to establish special controls to provide such assurance, but because the devices are not purported or represented to be for a use in supporting or sustaining human life or for a use which is of substantial importance in preventing impairment of human health, and do not present a potential

unreasonable risk of illness or injury, are to be regulated by general controls (section 513(a)(1)(A) of the FD&C Act). Class II devices are those devices for which general controls by themselves are insufficient to provide reasonable assurance of safety and effectiveness, and for which there is sufficient information to establish special controls to provide such assurance, including the promulgation of performance standards, postmarket surveillance, patient registries, development and dissemination of guidelines, recommendations, and other appropriate actions the Agency deems necessary to provide such assurance (section 513(a)(1)(B) of the FD&C Act). Class III devices are those devices for which insufficient information exists to determine that general controls and special controls would provide a reasonable assurance of safety and effectiveness, and are purported or represented to be for a use in supporting or sustaining human life or for a use which is of substantial importance in preventing impairment of human health, or present a potential unreasonable risk of illness or injury (section 513(a)(1)(C) of the FD&C Act).

Devices that were not in commercial distribution prior to May 28, 1976 (generally referred to as postamendments devices) are automatically classified by section 513(f)(1) of the FD&C Act into class III without any FDA rulemaking process. Those devices remain in class III and require premarket approval, unless, and until, (1) FDA reclassifies the device into class I or class II, or (2) FDA issues an order finding the device to be substantially equivalent, in accordance with section 513(i) of the FD&C Act, to a predicate device that does not require premarket approval. FDA determines whether new devices are substantially equivalent to predicate devices by means of premarket notification procedures in section 510(k) of the FD&C Act and part 807 (21 CFR part 807), subpart E, of the regulations.

A postamendments device that has been initially classified in class III under section 513(f)(1) of the FD&C Act may be reclassified into class I or II under section 513(f)(3) of the

FD&C Act. Section 513(f)(3) of the FD&C Act provides that FDA, acting by administrative order, can reclassify the device into class I or class II on its own initiative, or in response to a petition from the manufacturer or importer of the device. To change the classification of the device, the proposed new class must have sufficient regulatory controls to provide a reasonable assurance of the safety and effectiveness of the device for its intended use.

FDA relies upon "valid scientific evidence," as defined in section 513(a)(3) and 21 CFR 860.7(c)(2), in the classification process to determine the level of regulation for devices. To be considered in the reclassification process, the "valid scientific evidence" upon which the Agency relies must be publicly available (see section 520(c) of the FD&C Act). Publicly available information excludes trade secret and/or confidential commercial information, e.g., the contents of a pending PMA (see section 520(c) of the FD&C Act).

In accordance with section 513(f)(3) of the FD&C Act, the Agency is issuing this proposed order to reclassify HIV serological diagnostic and supplemental tests and HIV NAT diagnostic and supplemental tests, postamendments class III devices, into class II (special controls), subject to premarket notification because the Agency believes the standard in section 513(a)(1)(B) of the FD&C Act is met because there is sufficient information to establish special controls, in addition to general controls, to provide reasonable assurance of the safety and effectiveness of the device.¹

¹ In December 2019, FDA began adding the term "Proposed amendment" to the "ACTION" caption for these documents, typically styled "Proposed order", to indicate that they "propose to amend" the Code of Federal Regulations. This editorial change was made in accordance with the Office of Federal Register's (OFR) interpretations of the Federal Register Act (44 U.S.C. chapter 15), its implementing regulations (1 CFR 5.9 and parts 21 and 22), and the Document Drafting Handbook.

Section 510(m) of the FD&C Act provides that a class II device may be exempted from the premarket notification requirements under section 510(k) of the FD&C Act if the Agency determines that premarket notification is not necessary to provide reasonable assurance of the safety and effectiveness of the device. FDA has determined that premarket notification is necessary to reasonably assure the safety and effectiveness of HIV serological diagnostic and supplemental tests and HIV NAT diagnostic and supplemental tests. Therefore, the Agency does not intend to exempt this proposed class II device from premarket notification (510(k)) submission under section 510(m) of the FD&C Act.

II. Regulatory History of the Devices

This proposed order covers HIV serological diagnostic and supplemental tests and HIV NAT diagnostic and supplemental tests. These are prescription tests that are assigned product code MZF. These postamendments devices are currently regulated as class III devices under section 513(f)(1) of the FD&C Act. Based on our review experience and consistent with the FD&C Act and FDA's regulations in 21 CFR 860.134, FDA believes that these devices should be reclassified from class III into class II with special controls because there is sufficient information for these devices to establish special controls that can provide a reasonable assurance of the device's safety and effectiveness.

FDA has regulated the devices subject to this proposed order for many years. The first serological test intended for use as an aid in the diagnosis of infection with HIV was approved in 1987. The first supplemental test intended for use as an aid in confirming diagnosis of infection with HIV was approved in 1992. Currently there are 11 diagnostic serological tests and 6 supplemental serological tests on the market in the United States. In 2006, FDA approved one

NAT test that is intended for use as an aid in the diagnosis of infection with HIV. This device is also approved as a supplemental NAT test.

A review of the medical device reporting databases indicates that there is a low number of reported events for HIV serological diagnostic and supplemental tests and HIV NAT diagnostic tests. Over 100 million HIV tests subject to this proposed reclassification have been sold since 2000, with less than 1,000 reported events as of September 2019. Of these, fewer than 40 are reported to involve injuries due to false results; the remainder are malfunctions, user errors, or incorrect results that had no reported effect on the individual being tested. There have been less than 10 recalls specific to these tests, and no class I recalls, indicating a good safety record for this device class.

III. Device Description

This proposed order applies to certain HIV serological diagnostic and supplemental tests that are prescription devices for the qualitative detection of HIV antigens and/or antibodies against HIV in human body fluids or tissues. As such, the prescription device must satisfy prescription labeling requirements for in vitro diagnostic products (see 21 CFR 809.10(a)(4) and (b)(5)(ii)). The tests are intended for use as an aid in the diagnosis of infection with HIV. These devices are not intended for monitoring patient status or for screening donors of blood, plasma, or human cells, tissues, or cellular or tissue-based products (HCT/Ps). HIV serological tests detect the presence of HIV by using anti-HIV antibodies and/or HIV antigens to detect the presence of HIV antigens and/or anti-HIV antibodies in human fluids. The analytes are detected by chemical, fluorescent, luminescent, or other methods to produce a qualitative output that determines the presence or absence of HIV in the sample. Supplemental serological tests are intended to be used as an additional test to confirm the presence of HIV antibodies or antigens in

specimens found to be repeatedly reactive by a diagnostic screening device. These tests are intended for professional use only.

This proposed order also applies to certain HIV NAT diagnostic and supplemental tests that are prescription devices for the detection of HIV nucleic acid in human body fluids or tissues. The tests are intended for use as an aid in the diagnosis of infection with HIV. These devices are not intended for monitoring patient status, or for screening donors of blood, plasma, or HCT/Ps. HIV NAT tests detect the presence of HIV by detecting HIV nucleic acid in human body fluids or from solutions after isolation of nucleic acid from cells or tissues. The nucleic acids are amplified and detected by labeled probes that produce a qualitative signal that indicates the presence or absence of HIV nucleic acid in the sample. Supplemental NAT tests are intended to be used as an additional test to confirm the presence of HIV nucleic acid in specimens found to be repeatedly reactive by a diagnostic screening device. These tests are intended for professional use only.

IV. Proposed Reclassification

FDA is proposing to reclassify HIV serological diagnostic and supplemental tests and HIV NAT diagnostic and supplemental tests. FDA held a public meeting on July 19, 2018, of the Blood Products Advisory Committee, convened as a medical device Panel ("the Panel"), which unanimously agreed that special controls, in addition to general controls, are sufficient to mitigate the risks to health from HIV serological diagnostic and supplemental tests and HIV NAT diagnostic and supplemental tests. The Panel believed that class II with special controls would provide reasonable assurance of the safety and effectiveness of the device. The Panel discussed the proposed special controls (see section VII), especially the performance criteria and number of samples that would be required for testing. The Panel also recommended that FDA

consider reclassification from class III to class II of HIV viral load tests indicated for use for monitoring patient status.

The Agency believes that, at this time, sufficient data and information exist such that the risks to health identified in section V can be mitigated by establishing special controls that, together with general controls, can provide a reasonable assurance of the safety and effectiveness of these devices. Therefore, FDA proposes these devices be reclassified from class III to class II.

In accordance with section 513(f)(3) of the FD&C Act and 21 CFR part 860, subpart C, FDA is proposing to reclassify postamendments HIV serological diagnostic and supplemental tests and NAT diagnostic and supplemental tests from class III into class II. FDA believes that there are sufficient data and information available through FDA's accumulated experience with these devices from review submissions, recommendations provided by the Panel, and from published literature to demonstrate that the proposed special controls, along with general controls, would effectively mitigate the risks to health identified in section V and provide a reasonable assurance of safety and effectiveness of these devices. Absent the special controls identified in this proposed order, general controls applicable to the device are insufficient to provide reasonable assurance of the safety and effectiveness of the device. FDA expects that the reclassification of these devices would enable more manufacturers to develop HIV serological diagnostic and supplemental and NAT diagnostic and supplemental tests such that patients would benefit from increased access to safe and effective tests.

FDA is proposing to create separate classification regulations for HIV serological diagnostic and supplemental tests and HIV NAT diagnostic and supplemental tests that will be reclassified from class III to class II. Under this proposed order, if finalized, HIV serological diagnostic and supplemental tests and HIV NAT diagnostic and supplemental tests will be

identified as prescription devices. In this proposed order the Agency has proposed the special controls under section 513(a)(1)(B) of the FD&C Act that, together with general controls, would provide a reasonable assurance of the safety and effectiveness of HIV serological and NAT diagnostic and supplemental tests.

Section 510(m) of the FD&C Act provides that FDA may exempt a class II device from the premarket notification requirements under section 510(k) of the FD&C Act if FDA determines that premarket notification is not necessary to provide reasonable assurance of the safety and effectiveness of the device. For these HIV serological diagnostic and supplemental tests and HIV NAT diagnostic and supplemental tests, FDA has determined that premarket notification is necessary to provide a reasonable assurance of the safety and effectiveness of the devices. Therefore, FDA does not intend to exempt these proposed class II devices from the 510(k) requirements. If this proposed order is finalized, persons who intend to market this type of device must submit to FDA a 510(k) and receive clearance prior to marketing the device.

This proposal, if finalized, will decrease regulatory burden on industry, as manufacturers will no longer have to submit a PMA for these types of devices but can instead submit a 510(k) to the Agency for review prior to marketing their device. A 510(k) is a less burdensome pathway to market a device, which typically results in a shorter premarket review timeline compared to a PMA. This ultimately provides more timely access of these types of devices to patients.

V. Risks to Health

HIV can be transmitted to others by blood transfusion, sex, sharing of contaminated needles by intravenous drug users, and from mother to child during pregnancy, childbirth, and breast feeding (Ref. 1). Left untreated, a significant proportion of those infected with HIV will develop acquired immunodeficiency syndrome (AIDS), which causes significant morbidity and

mortality. However, with consistent anti-retroviral treatment, HIV infection is a treatable, chronic condition with significantly improved survival and quality of life for people living with HIV and significantly decreased risk of transmission to others (Ref. 2). The Centers for Disease Control and Prevention (CDC) recommends that all persons ages 13 through 64 and pregnant women be tested at least once, with more frequent testing for individuals at high risk of infection. Nevertheless, at the present time, only about 85 percent of people infected with HIV in the United States know that they are infected, and those who do not know their status are many times more likely to transmit the virus to others (Ref. 3). Therefore, improving access to HIV diagnostic devices is an urgent public health priority. After considering the recommendations of the panel, FDA's accumulated experience with these devices from review submissions, and the published literature, FDA has identified the following probable risks to health associated with HIV serological diagnostic and supplemental tests:

(1) A false negative/false non-reactive test result may influence patient management decisions, such as the withholding or discontinuation of antiretroviral therapy, which can lead to serious injury including death. A false negative/false non-reactive test result also may contribute to public health risk by leading to inadvertent transmission of virus by an infected person. Factors that may cause decreased test sensitivity and/or increased rate of false negative/false non-reactive test reporting include, but are not limited to, strain variability, acquisition of de novo mutations in genomic regions of HIV targeted by the device, the presence of interfering substances in the sample, acute infection at a stage that is too early for a device to detect the infection, and analyte concentrations that are too low to be detected by the device due to suppression of analyte expression by drugs used to treat or prevent HIV infection. False negative/false non-reactive results also can be caused by improper sample collection or sample

handling, loss of sensitivity of the device, failure of detection reagents, and failure of instruments. They also can be caused by misinterpretation of invalid results as negative.

(2) A false positive/false reactive test result may contribute to unnecessary initiation of treatment. It can also lead to unnecessary interventions such as an unnecessary Caesarian section for women during childbirth, unnecessary treatment of infants with anti-retroviral medications, withholding of breastfeeding, and significant emotional stress. Factors that may lead to false positive/false reactive results include cross-reactivity with other substances in the sample, contamination of the sample, patient participation in vaccine trials, and improper sample handling and instrument use.

VI. Summary of the Reasons for Reclassification

FDA believes that HIV serological diagnostic and supplemental tests and HIV NAT diagnostic and supplemental tests should be reclassified from class III (PMA) into class II (special controls) because special controls, in addition to general controls, can be established to mitigate the risks to health identified in section V and provide reasonable assurance of the safety and effectiveness of these device types. The proposed special controls are identified by FDA in section VII. FDA's reasons for reclassification are as follows:

(1) There is substantial scientific and medical information available regarding the nature, complexity, and risks associated with HIV serological diagnostic and supplemental tests and NAT diagnostic and supplemental tests. The safety and effectiveness of this device type has been well-established by the performance of the more than 20 devices currently available (Ref. 4).

(2) Risks associated with the failure of the device to perform as indicated (e.g., false negative/false non-reactive or false positive/false reactive test results) can be mitigated through a

combination of special controls, including performance criteria and requirements for submission of certain aspects of labeling, submission of certain manufacturing information, and submission of a complaint log. Performance criteria will consist primarily of analytical and clinical study design specifications and performance criteria that are based on public information regarding the performance and validation of previously approved devices. Examples of labeling mitigations include appropriate limitations, including that results should be confirmed according to current guidelines as promulgated by the CDC and other public health authorities, which are necessary to ensure that the devices are used and the results are interpreted appropriately, given the diversity of environments in which they are intended to be used. Manufacturing information submitted will include summaries of strategies to detect new types, subtypes, genotypes and mutations to ensure the tests continue to detect clinically relevant forms of HIV, a summary of the design matrix that determines the severity of events to ensure appropriate adverse event reporting, protocols for assessing stability, evaluation of test performance at the extremes of specifications to ensure the tests have been validated to function correctly under diverse conditions. The complaint log that will be submitted annually for 5 years following clearance of a traditional 510(k) is the log required to be maintained by device manufacturers under 21 CFR 820.198(a). We are proposing as a special control to require submission of all complaints, whether or not the complaint was reported under part 803 (21 CFR part 803). We are not requiring submission of an annual report as described in 21 CFR 814.84. Review of the complaint log will allow FDA to closely monitor issues with manufacturing and implementation of new devices that may not rise to the level of adverse event reporting required under 21 CFR 820.198(a) but that may have an effect on the performance of the devices.

Taking into account the probable health benefits of the use of the device and the nature and known incidence of the risk of the device, FDA, on its own initiative, is proposing to reclassify these postamendments devices from class III into class II. FDA believes that, when used as indicated, HIV serological and NAT diagnostic and supplemental tests can provide significant benefits to clinicians and patients.

VII. Proposed Special Controls

FDA believes that these devices can be classified into class II with the establishment of special controls. FDA believes that these special controls, in addition to general controls, will provide a reasonable assurance of the safety and efficacy of these devices. Tables 1 and 2 demonstrate how these proposed special controls will mitigate each of the identified risks to health in section V.

Table 1.--Risks to Health and Mitigation Measures for HIV Serological Diagnostic and Supplemental Tests

Identified Risks to Health	Mitigation Measures
<p>A false negative/false non-reactive test result may influence patient management decisions, such as the withholding of antiviral therapy, which can lead to serious injury including death.</p> <p>A false negative/false non-reactive test result may contribute to public health risk by leading to inadvertent transmission of virus by an infected person.</p>	<p>Labeling limitations, warnings, and interpretation requirements</p> <p>Analytical and clinical sensitivity performance criteria</p> <p>Clinical testing on appropriate populations</p> <p>Acceptable strategies for monitoring emergence of and ability of the test to detect new or altered circulating forms of HIV</p> <p>Acceptable processes for failure mode analysis, testing performance at extremes of specifications, determining severity of adverse events and malfunctions</p> <p>Submission of a complaint log to monitor decreases in test performance or manufacturing failures</p>
<p>A false positive/false reactive test result may contribute to unnecessary initiation of treatment or other medical interventions, which increases patient risk to the potential adverse effects of such treatments or medical interventions.</p>	<p>Labeling instructions for appropriate confirmation of results</p> <p>Analytical and clinical specificity performance criteria</p> <p>Clinical testing on appropriate populations</p> <p>Acceptable validation of susceptibility to interference and cross-reactivity</p> <p>Acceptable processes for failure mode analysis, testing</p>

	performance at extremes of specifications, determining severity of adverse events and malfunctions Submission of a complaint log to monitor trends in false positive results
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Table 2.--Risks to Health and Mitigation Measures for HIV NAT Diagnostic and Supplemental Tests

Identified Risks to Health	Mitigation Measures
A false negative/false non-reactive test result may influence patient management decisions, such as the withholding of antiviral therapy, which can lead to serious injury including death. A false negative/false non-reactive test result may contribute to public health risk by leading to inadvertent transmission of virus by an infected person.	Labeling limitations, warnings, and interpretation requirements Analytical and clinical sensitivity performance criteria Clinical testing on appropriate populations Acceptable strategies for monitoring emergence of and ability of the test to detect new or altered circulating forms of HIV Acceptable processes for failure mode analysis, testing performance at extremes of specifications, determining severity of adverse events and malfunctions Submission of a complaint log to monitor decreases in test performance or manufacturing failures
A false positive/false reactive result may contribute to unnecessary initiation of treatment or other medical intervention, which increases patient risk to the potential adverse effects of such treatments or medical interventions.	Labeling instructions for appropriate confirmation of results Analytical and clinical specificity performance criteria Clinical testing on appropriate populations Acceptable validation of susceptibility to interference and cross-reactivity Acceptable processes for failure mode analysis, testing performance at extremes of specifications, determining severity of adverse events and malfunctions Submission of a complaint log to monitor trends in false positive results

If this proposed order is finalized, HIV serological diagnostic and supplemental tests and HIV NAT diagnostic and supplemental tests will be reclassified into class II (special controls). As discussed below, the reclassification will be codified in 21 CFR 866.3956 (serological) and 21 CFR 866.3957 (NAT) tests. Firms submitting a 510(k) for an HIV serological diagnostic and/or supplemental or HIV NAT diagnostic and/or supplemental test will be required to comply with the particular mitigation measures set forth in the special controls. Adherence to the special

controls, in addition to the general controls, is necessary to provide a reasonable assurance of the safety and effectiveness of the devices.

VIII. Analysis of Environmental Impact

The Agency has determined under 21 CFR 25.34(b) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

IX. Paperwork Reduction Act of 1995

FDA tentatively concludes that this proposed rule contains no new collection of information. Therefore, clearance by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (PRA) (44 U.S.C. 3501-3521) is not required. This proposed order refers to previously approved FDA collections of information. These collections of information are subject to review by the OMB under the PRA. The collections of information in part 807, subpart E, regarding premarket notification submissions have been approved under OMB control number 0910-0120; the collections of information in 21 CFR part 820 have been approved under OMB control number 0910-0073; and the collections of information in 21 CFR parts 801 and 809 have been approved under OMB control number 0910-0485.

X. Codification of Orders

Under section 513(f)(3) of the FD&C Act, FDA may issue final orders to reclassify devices. FDA will continue to codify classifications and reclassifications in the Code of Federal Regulations (CFR). Changes resulting from final orders will appear in the CFR as newly codified orders. Therefore, under section 513(f)(3), in the proposed order, we are proposing to codify HIV serological diagnostic and/or supplemental tests in the new 21 CFR 866.3956, under which HIV serological diagnostic and/or supplemental tests would be reclassified from class III

to class II, and HIV NAT diagnostic and/or supplemental tests in the new 21 CFR 866.3957, under which HIV NAT diagnostic and/or supplemental tests would be reclassified from class III to class II.

XI. Proposed Effective Date

FDA proposes that any final order based on this proposed order become effective 30 days after its date of publication in the *Federal Register*.

XII. References

The following references have been placed on display in the Dockets Management Staff (see ADDRESSES) and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday; they are also available electronically at <https://www.regulations.gov>. FDA has verified the website addresses, as of the date this document publishes in the *Federal Register*, but websites are subject to change over time.

1. Branson, B.M., H.H. Handsfield, M.A. Lampe, et al., "Revised Recommendations for HIV Testing of Adults, Adolescents, and Pregnant Women in Health-Care Settings," *MMWR. Recommendations and Reports: Morbidity and Mortality Weekly Report*, 55(RR14): 1-17, 2007.
2. Collaboration, T.A.T.C., "Survival of HIV-Positive Patients Starting Antiretroviral Therapy Between 1996 and 2013: A Collaborative Analysis of Cohort Studies," *Lancet HIV*, 2017.
3. Dailey, A.F., B.E. Hoots, H.I. Hall, et al., "Vital Signs: Human Immunodeficiency Virus Testing and Diagnosis Delays--United States," *MMWR. Recommendations and Reports: Morbidity and Mortality Weekly Report*, 66: 1300-1306, 2017.
4. "Reclassification of HIV Point of Care and Laboratory-Based Serological and NAT Diagnostic Devices from Class III (PMA) to Class II 510(k); Issue Summary; Prepared for the

July 19, 2018, Meeting of the Blood Products Advisory Committee (BPAC))." Available at: <https://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/BloodVaccinesandOtherBiologics/BloodProductsAdvisoryCommittee/ucm597841.htm>.

List of Subjects in 21 CFR Part 866

Biologics, Laboratories, Medical devices.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, it is proposed that 21 CFR part 866 be amended as follows:

PART 866--IMMUNOLOGY AND MICROBIOLOGY DEVICES

1. The authority citation for part 866 continues to read as follows:

Authority: 21 U.S.C. 351, 360, 360c, 360e, 360j, 360l, 371.

2. Add § 866.3956 to subpart D to read as follows:

§ 866.3956 Human immunodeficiency virus (HIV) serological diagnostic and/or supplemental test.

(a) *Identification.* Human immunodeficiency virus (HIV) serological diagnostic and supplemental tests are prescription devices for the qualitative detection of HIV antigen(s) and/or detection of antibodies against HIV in human body fluids or tissues. The tests are intended for use as an aid in the diagnosis of infection with HIV. The test results are intended to be interpreted in conjunction with other relevant clinical and laboratory findings. For professional use only. These tests are not intended to be used for monitoring patient status, or for screening donors of blood, plasma, or human cells, tissues, and cellular and tissue-based products (HCT/Ps).

- (b) *Classification.* Class II (special controls). The special controls for this device are:

(1) For all HIV serological diagnostic and supplemental tests

(i) The labeling must include:

(A) An intended use that states that the device is not intended for use for screening donors of blood, plasma, or HCT/Ps.

(B) A detailed explanation of the principles of operation and procedures used for performing the assay.

(C) A detailed explanation of the interpretation of results and recommended actions to take based on results.

(D) Limitations, which must be updated to reflect current clinical practice and disease presentation and management. The limitations must include, but are not limited to, statements that indicate:

(1) The matrices with which the device has been cleared, and that use of this test kit with specimen types other than those specifically cleared for this device may result in inaccurate test results.

(2) The test is not intended to be used to monitor individuals who are undergoing treatment for HIV infection.

(3) A specimen with a reactive result should be investigated further following current guidelines.

(4) All test results should be interpreted in conjunction with the individual's clinical presentation, history, and other laboratory results.

(5) A test result that is nonreactive does not exclude the possibility of exposure to or infection with HIV. Nonreactive results in this assay may be due to analyte levels that are below the limit of detection of this assay.

(ii) Device verification and validation must include:

(A) Detailed device description, including the device components, ancillary reagents required but not provided, and an explanation of the methodology. Additional information appropriate to the technology must be included such as the amino acid sequence of antigen(s) and design of capture antibodies.

(B) For devices with assay calibrators, the design of all primary, secondary, and subsequent quantitation standards used for calibration as well as their traceability to a reference material. In addition, analytical testing must be performed following the release of a new lot of the standard material that was used for device clearance, or when there is a transition to a new calibration standard.

(C) Detailed documentation of analytical performance studies conducted as appropriate to the technology, specimen types tested, and intended use of the device, including, but not limited to, limit of blank, limit of detection, cutoff determination, precision, endogenous and exogenous interferences, cross reactivity, carry-over, quality control, matrix equivalency, and sample and reagent stability. Samples selected for use in analytical studies or used to prepare samples for use in analytical studies must be from subjects with clinically relevant circulating genotypes in the United States.

(D) Multisite reproducibility study that includes the testing of three independent production lots.

(E) Analytical sensitivity of the test must be the same as or better than that of other cleared or approved tests. Samples tested must include appropriate numbers and types of samples, including real clinical samples near the lower limit of detection. Analytical specificity of the test must be the same as or better than that of other cleared or approved tests. Samples

must include appropriate numbers and types of samples from patients with different underlying illnesses or infections and from patients with potential endogenous interfering substances.

(F) Detailed documentation of performance from a multisite clinical study. Performance must be analyzed relative to an FDA-cleared or approved comparator. This study must be conducted using patient samples, with an appropriate number of HIV positive and HIV negative samples in applicable risk categories. Additional subgroups or types must be validated using appropriate numbers and types of samples. The samples may be a combination of fresh and repository samples, sourced from within and outside the United States, as appropriate. The study designs, including number of samples tested, must be sufficient to meet the following criteria:

(1) Clinical sensitivity of the test must have a lower bound of the 95 percent confidence interval of greater than or equal to 99 percent.

(2) Clinical specificity of the test must have a lower bound of the 95 percent confidence interval of greater than or equal to 99 percent.

(G) Strategies for detection of new strains, types, subtypes, genotypes, and genetic mutations as they emerge.

(H) Risk analysis and management strategies, such as Failure Modes Effects Analysis and/or Hazard Analysis and Critical Control Points summaries and their impact on test performance.

(I) Final release criteria to be used for manufactured test lots with appropriate evidence that lots released at the extremes of the specifications will meet the claimed analytical and clinical performance characteristics as well as the stability claims.

(J) All stability protocols, including acceptance criteria.

(K) Proposed procedure(s) for evaluating customer complaints and other device information that determines when to submit a medical device report.

(L) Premarket notification submissions must include the information contained in paragraph (b)(1)(ii)(A) through (K) of this section.

(iii) Manufacturers must submit a log of all complaints. The log must include the following information regarding each complaint: the type of event (false negative/false non-reactive or false positive/false reactive), lot, date, population, and whether or not the complaint was reported under part 803 of this chapter (Medical Device Reporting). The log must be submitted annually on the anniversary of clearance, for 5 years following initial clearance of a new traditional 510(k).

(2) If the test is intended for Point of Care (PoC) use, the following special controls, in addition to those listed in paragraph (b)(1) of this section apply:

(i) The intended use must include a statement that the test is for PoC use.

(ii) The PoC intended use must include the following information:

(A) That distribution of the test is limited to clinical laboratories that have an adequate quality assurance program, including planned systematic activities that provide adequate confidence that requirements for quality will be met and where there is assurance that operators will receive and use the instructional materials.

(B) That the test is for use only by an agent of a clinical laboratory.

(C) That individuals must receive the "Subject Information Notice" prior to specimen collection and appropriate information when test results are provided.

(iii) PoC labeling must include instructions to follow current guidelines for informing the individual of the test result and its interpretation.

(iv) The instructions must state that reactive results are considered preliminary and should be confirmed following current guidelines.

(v) Device verification and validation for the PoC claim must include:

(A) Detailed documentation of performance from a multisite clinical study. Performance must be analyzed relative to an FDA cleared or approved comparator. This study must be conducted using patient samples, with appropriate numbers of HIV positive and HIV negative samples in applicable risk categories. Additional subgroup or type claims must be validated using appropriate numbers and types of samples. The samples may be a combination of fresh and repository samples, sourced from within and outside the United States, as appropriate. If the test is intended solely for PoC use, the test must meet only the performance criteria in paragraph (b)(2)(v)(A)(1) and (2) of this section and not the criteria in paragraph (b)(1)(ii)(F) of this section:

(1) Clinical sensitivity of the test must have a lower bound of the 95 percent confidence interval of greater than or equal to 98 percent.

(2) Clinical specificity of the test must have a lower bound of the 95 percent confidence interval of greater than or equal to 98 percent.

(B) Premarket notification submissions must include the information contained in paragraph (b)(2)(v)(A) of this section.

(3) If the test is intended for supplemental use in addition to use as an aid in initial diagnosis, the following special controls, in addition to those listed in paragraphs (b)(1) and (2) of this section, as appropriate, apply:

(i) For the additional supplemental claim, a clinical study must be performed that includes samples that were initially reactive and repeatedly reactive on a diagnostic test but were negative or indeterminate on a different confirmatory test.

(ii) The intended use must include a statement that the test is intended for use as an additional test to confirm the presence of HIV antibodies or antigens in specimens found to be repeatedly reactive by a diagnostic screening test.

(4) If the test is intended solely as a supplemental test, the following special controls, in addition to those listed in paragraphs (b)(1) and (2) of this section, except those in paragraphs (b)(1)(ii)(F) and (b)(2)(v)(A) of this section, as appropriate, apply:

(i) The labeling must include a statement that the test is intended for use as an additional test to confirm the presence of HIV antibodies or antigens in specimens found to be repeatedly reactive by a diagnostic screening test.

(ii) The labeling must clearly state that the test is not for use for initial diagnosis or is not intended as a first-line test.

(iii) A clinical study must be performed that includes samples that were initially reactive and repeatedly reactive on a diagnostic test but were negative or indeterminate on a confirmatory test.

(5) If the test is intended to differentiate different HIV types, the following special controls, in addition to those listed in paragraphs (b)(1) through (4) of this section, as appropriate, apply:

(i) The labeling must include the statement that the test is intended for the confirmation of initial results from a diagnostic test and differentiation of different HIV types.

(ii) Analytical and clinical sensitivity and specificity for each of the HIV types, strains, and subtypes of HIV intended to be differentiated must be evaluated.

(iii) The results interpretation must include instructions for the user on how to interpret the results, including un-typeable and co-infection results.

3. Add § 866.3957 to subpart D to read as follows:

§ 866.3957 Human immunodeficiency virus (HIV) nucleic acid (NAT) diagnostic and/or supplemental test.

(a) *Identification.* Human immunodeficiency virus (HIV) nucleic acid (NAT) diagnostic and supplemental tests are prescription devices for the qualitative detection of HIV nucleic acid in human body fluids or tissues. The tests are intended for use as an aid in the diagnosis of infection with HIV. The test results are intended to be interpreted in conjunction with other relevant clinical and laboratory findings. For prescription use only. These tests are not intended to be used for monitoring patient status, or for screening donors of blood, plasma, or human cells, tissues, or cellular or tissue-based products (HCT/Ps).

(b) *Classification.* Class II (special controls). The special controls for this device are:

(1) For all HIV NAT diagnostic and/or supplemental tests

(i) The labeling must include:

(A) An intended use that states that the device is not intended for use for screening donors of blood, plasma, or HCT/Ps.

(B) A detailed explanation of the principles of operation and procedures used for performing the assay.

(C) A detailed explanation of the interpretation of results and recommended actions to take based on results.

(D) Limitations, which must be updated to reflect current clinical practice and disease presentation and management. The limitations must include, but are not limited to, statements that indicate:

(1) The matrices with which the device has been cleared, and that use of this test kit with specimen types other than those specifically cleared for this device may result in inaccurate test results.

(2) The test is not intended to be used to monitor individuals who are undergoing treatment for HIV infection.

(3) A specimen with a reactive result should be investigated further following current guidelines.

(4) All test results should be interpreted in conjunction with the individual's clinical presentation, history, and other laboratory results.

(5) A test result that is nonreactive does not exclude the possibility of exposure to or infection with HIV. Nonreactive results in this assay may be due to analyte levels that are below the limit of detection of this assay.

(ii) Device verification and validation must include:

(A) Detailed device description, including the device components, ancillary reagents required but not provided, and an explanation of the methodology. Additional information appropriate to the technology must be included such as design of primers and probes.

(B) For devices with assay calibrators, the design and nature of all primary, secondary, and subsequent quantitation standards used for calibration as well as their traceability to a reference material. In addition, analytical testing must be performed following the release of a

new lot of the standard material that was used for device clearance, or when there is a transition to a new calibration standard.

(C) Detailed documentation of analytical performance studies conducted as appropriate to the technology, specimen types tested, and intended use of the device, including, but not limited to, limit of blank, limit of detection, cutoff determination, precision, endogenous and exogenous interferences, cross reactivity, carry-over, quality control, matrix equivalency, and sample and reagent stability. Samples selected for use in analytical studies or used to prepare samples for use in analytical studies must be from subjects with clinically relevant circulating genotypes in the United States. The effect of each claimed nucleic-acid isolation and purification procedure on detection must be evaluated.

(D) Multisite reproducibility study that includes the testing of three independent production lots.

(E) Analytical sensitivity of the test must be the same as or better than that of other cleared or approved tests. Samples tested must include appropriate numbers and types of samples, including real clinical samples near the lower limit of detection. Analytical specificity of the test must be as the same as or better than that of other cleared or approved tests. Samples must include appropriate numbers and types of samples from patients with different underlying illnesses or infections and from patients with potential endogenous interfering substances.

(F) Detailed documentation of performance from a multisite clinical study. Performance must be analyzed relative to an FDA cleared or approved comparator. This study must be conducted using appropriate patient samples, with appropriate numbers of HIV positive and negative samples in applicable risk categories. Additional subtype, strain, or types must be validated using appropriate numbers and types of samples. The samples may be a combination

of fresh and repository samples, sourced from within and outside the United States, as appropriate. The study designs, including number of samples tested, must be sufficient to meet the following criteria:

(1) Clinical sensitivity of the test must have a lower bound of the 95 percent confidence interval of greater than or equal to 99 percent.

(2) Clinical specificity of the test must have a lower bound of the 95 percent confidence interval of greater than or equal to 99 percent.

(G) Strategies for detection of new strains, types, subtypes, genotypes, and genetic mutations as they emerge.

(H) Risk analysis and management strategies, such as Failure Modes Effects Analysis and/or Hazard Analysis and Critical Control Points summaries and their impact on test performance.

(I) Final release criteria to be used for manufactured test lots with appropriate evidence that lots released at the extremes of the specifications will meet the claimed analytical and clinical performance characteristics as well as the stability claims.

(J) All stability protocols, including acceptance criteria.

(K) Proposed procedure(s) for evaluating customer complaints and other device information that determine when to submit a medical device report.

(L) Premarket notification submissions must include the information contained in paragraph (b)(1)(ii)(A) through (K) of this section.

(iii) Manufacturers must submit a log of all complaints. The log must include the following information regarding each complaint: the type of event (false negative/false non-reactive or false positive/false reactive), lot, date, population, and whether or not the complaint

was reported under part 803 of this chapter (Medical Device Reporting). The log must be submitted annually on the anniversary of clearance, for 5 years following initial clearance of a new traditional 510(k).

(2) If the test is intended for Point of Care (PoC) use, the following special controls, in addition to those listed in paragraph (b)(1) of this section, apply:

(i) The intended use must include a statement that the test is for PoC use.

(ii) The PoC intended use must include the following information:

(A) That distribution of the test is limited to clinical laboratories that have an adequate quality assurance program, including planned systematic activities that provide adequate confidence that requirements for quality will be met and where there is assurance that operators will receive and use the instructional materials.

(B) That the test is for use only by an agent of a clinical laboratory.

(C) That individuals must receive the "Subject Information Notice" prior to specimen collection and appropriate information when test results are provided.

(iii) PoC labeling must include instructions to follow current guidelines for informing the individual of the test result and its interpretation.

(iv) The instructions must state that reactive results are considered preliminary and should be confirmed following current guidelines.

(v) Device verification and validation for the PoC claim must include:

(A) Detailed documentation from a well-conducted multisite clinical study. Performance must be analyzed relative to an FDA cleared or approved comparator. This study must be conducted using patient samples, with appropriate numbers of HIV positive and HIV negative samples in applicable risk categories. Additional subgroup or type claims must be validated

using appropriate numbers and types of samples. The samples may be a combination of fresh and repository samples, sourced from within and outside the United States, as appropriate. If the test is intended solely for PoC use, the test must meet only the performance criteria in paragraphs (b)(2)(v)(A)(1) and (2) of this section and not the criteria in paragraph (b)(2)(ii)(F) of this section:

(1) Clinical sensitivity of the test must have a lower bound of the 95 percent confidence interval of greater than or equal to 98 percent.

(2) Clinical specificity of the test must have a lower bound of the 95 percent confidence interval of greater than or equal to 98 percent.

(B) Premarket notification submissions must include the information contained in paragraph (b)(2)(v)(A) of this section.

(3) If the test is intended for supplemental use in addition to use as an aid in initial diagnosis, the following special controls, in addition to those listed in paragraphs (b)(1) and (2) of this section, as appropriate, apply:

(i) For the additional supplemental claim, a clinical study must be performed that includes samples that were initially reactive and repeatedly reactive on a diagnostic test but were negative or indeterminate on a confirmatory test.

(ii) The intended use must include a statement that the test is intended for use as an additional test to confirm the presence of HIV viral nucleic acid in specimens found to be repeatedly reactive by a diagnostic screening test.

(4) If the test is intended solely as a supplemental test, the following special controls, in addition to those listed in paragraphs (b)(1) and (2) of this section, except those in paragraphs (b)(1)(ii)(F) and (b)(2)(v)(A) of this section, as appropriate, apply:

(i) The labeling must include a statement that the test is intended for use as an additional test to confirm the presence of HIV viral nucleic acid in specimens found to be repeatedly reactive by a diagnostic screening test.

(ii) The labeling must clearly state that the test is not for use for initial diagnosis or is not intended as a first-line test.

(iii) A clinical study must be performed that includes samples that were initially reactive and repeatedly reactive on a diagnostic test but were negative or indeterminate on a confirmatory test.

(5) If the test is intended to differentiate different HIV types, the following special controls, in addition to those listed in paragraphs (b)(1) through (4) of this section, as appropriate, apply:

(i) The labeling must include the statement that the test is intended for the confirmation of initial results and differentiation of different HIV types.

(ii) Analytical and clinical sensitivity and specificity for each of the types, strains, and subtypes of HIV intended to be differentiated must be evaluated.

(iii) The results interpretation must include instructions for the user on how to interpret the results, including un-typeable and co-infection results.

Dated: February 18, 2020.

Lowell J. Schiller,

Principal Associate Commissioner for Policy.

[FR Doc. 2020-03515 Filed: 2/20/2020 8:45 am; Publication Date: 2/21/2020]